28. The method according to claim 26, wherein said composition comprises at least 10^9 genomes rAAV.

29. The method according to claim 26, wherein the rAAV is substantially free of contamination with helper virus.

REMARKS

Claims 18 - 29 are pending.

Applicants and the undersigned attorney wish to thank Examiner Jill Martin for the courtesy extended in the telephone interview conducted on Tuesday, October 24, 2000. In that interview, proposed claim language and the cited prior art were discussed. This response addresses all of the points discussed in that interview, as well as those which were raised in the June 21, 2000 Office Action.

Claims 7, 16 and 17 have been canceled. The cancellation of these claims renders the rejections thereof moot.

Support for new claims 23 and 24 is found on page 44, line 12 - 16. Claim 25 is supported on page 7, lines 11-16. Support for claims 26 and 27 is found on page 12, lines 1-6 and in Example 7.

Example 7 demonstrates that injection of a composition containing rAAV expressing ApoE into ApoE knockout mice leads to muscle fiber transduction and secretion of substantial quantities of recombinant protein in the circulation. Prolonged expression of the transgene in the muscle fiber was observed in the absence of a destructive CTL immune response [page 44, lines 11-28]. ApoE knockout mice are accepted in the relevant art as an animal model which correlates with atherosclerosis in humans. See, e.g., the attached abstracts, J. Osada et al, "The value of apolipoprotein E knockout mice for studying the effects of dietary fat and cholesterol on atherogenesis", *Curr. Opin. Lipidol.*, 11(1):25-29 (Feb. 2000) and C. Desurmont, et al, "Complete atherosclerosis regression after human ApoE gene transfer in ApoE-deficient/nude mice", *Arterioscler. Thromb. Vasc. Biol.*, 20(2):435-442 (Feb. 2000). Although these abstracts published after the priority date to which

this application is entitled, they support the fact that one of skill in the art accepts ApoE-deficient mice as a relevant animal model of human atherosclerosis.

Claims 28 and 29 are supported on page 7, lines 11-16, Example 7, and by prior claim 22.

No new matter is added by this amendment.

I. Double-Patenting Rejection

Claims 16-22 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of US Patent No. 5,866,522.

Applicants request that this rejection be deferred until such time as the claims are considered to be otherwise in condition for allowance.

II. Rejections under 35 USC §102

Claims 16, 17, 19, 20, and 21 have been rejected under 35 USC §102(a) as being anticipated by Gouras et al, Neurobiology of Aging (1996).

Applicants have contacted the publisher of Gouras and have been informed that the cited document was released for publication on July 26, 1996. A copy of the communication received from the publisher is attached. This date is less than one year prior to the priority date to which this application is entitled.

Applicants submit herewith a Declaration pursuant to 37 CFR §1.131, which demonstrates invention of the subject matter claimed in the present application prior to the publication date of the cited reference. Accordingly, Gouras is not available as prior art.

Withdrawal of this rejection is requested.

III. Rejection Under 35 USC §103

Claims 16-22 are rejected under 35 USC §103(a) as being unpatentable over Podsakoff et al, US Patent 5,858,351, in view of Chiorini et al, US Patent 5,693,531.

Applicants respectfully traverse this rejection.

There is no teaching or suggestion in the cited prior art of a pharmaceutical composition containing rAAV encoding apolipoprotein for delivery directly to a subject. Nor is there any teaching or suggestion in the cited prior art of a method for expressing ApoE for the treatment of atherosclerosis .

Podsakoff refers to the construction of an AAV vector containing erythropoietin. Podsakoff does not teach or suggest the use of ApoE. Nor does Podsakoff teach or suggest any treatment for atherosclerosis.

As noted by the examiner, Podsakoff teaches an assay to determine the presence of rAAV-contamination with adenoviruses. However, Podsakoff lacks a teaching of the purification method disclosed in the present application which achieves the level of purity which permits the rAAV compositions of the invention to achieve expression "in the absence of a cytotoxic immune response directed against the cell". [See, the description of purification in Podsakoff at column 18, lines 20-35].

More particularly, the present application discloses the use of four rounds of cesium chloride density gradient centrifugation using the techniques described by Fisher et al, J. Virol, 70:520-532 (1996). See, e.g., page 15, lines 25 - 29 of the specification. In addition, the specification utilizes this production method in the Examples which describe generation of rAAV encoding Factor IX and rAAV encoding ApoE [see, Example 7, page 34, lines 17-21, and page 43, lines 29-32].

Absent any teaching or suggestion of this purification method in Podsakoff, Applicants believe that it is not possible to draw the conclusion that Podsakoff achieves the level of purity which is achieved using the methods described in the present invention. Similarly, it is not possible to draw from Podsakoff the conclusion that Podsakoff can achieve expression in the absence of a cytotoxic immune response directed against the cell.

Chiorini refers to transducing AAV particles into eukaryotic cells *in vitro* and delivering the rAAV-transduced cells to a subject for therapeutic purposes. Chiorini does *not* teach or suggest the use of rAAV particles for direct administration to a subject. In fact, Chiorini actually teaches away from delivering rAAV directly to a subject.

The combination of Podsakoff and Chiorini teaches away from the use of rAAV containing ApoE for delivery directly into the human body. Thus, one of skill in the art would *not* have been motivated to make a pharmaceutical composition containing rAAV expressing ApoE and a carrier, nor would there have been any expectation that such a composition would be successful. Similarly, there would have been no motivation to deliver ApoE using a composition of the invention, nor would there have been any expectation of success that such a composition could successfully deliver and express ApoE.

For these reasons, Applicants request withdrawal and reconsideration of this rejection.

Supplemental Information Disclosure Statement (IDS)

Applicants are submitting herewith a Supplemental IDS which presents the prior art cited by Examiner Shukla in co-pending Application No. 09/237,064. A copy of this co-pending application is also provided.

The Director of the US Patent and Trademark Office is authorized to charge any deficiency in the fee associated with the filing of this paper to deposit account 08-3040.

Respectfully submitted,

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